REMARKS

Claims 1-16 have been amended in order to write these claims in the appropriate U.S. claim format.

Claims 8 and 15 have been amended in order to limit the multiple dependencies of these claims.

Claims 32-34 have been added by the foregoing amendments. Support for claim 32 occurs, for example, in original claim 8; support for claim 33 occurs, for example, in original claim 15; and support for claim 34 occurs, for example, in original claim 16.

Claims 1-34 remain in the application.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Date: January 9, 2002

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Version With Markings to Show Changes Made

In the specification:

The following Abstract of the disclosure has been provided as a new page 108:

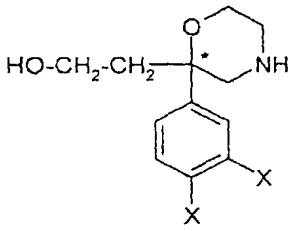
ABSTRACT

The invention relates to a process for the preparation of substituted 2-(2-arylmorpholin-2-yl)ethanol derivatives.

In the Claims:

Claims 1-16 have been amended as follows:

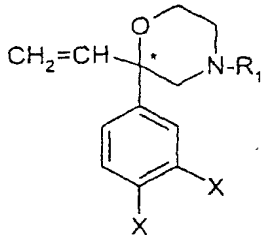
1. A process for the preparation of a compound, in the enantiomerically pure form, of formula:

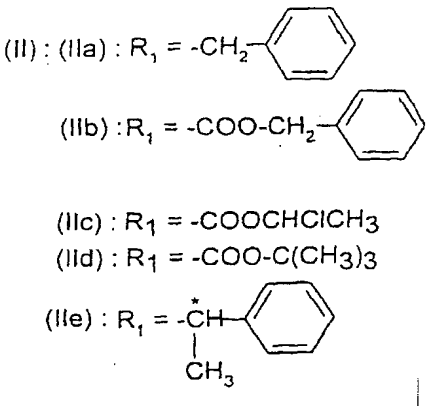


(I)

in which X represents a halogen atom, of its salts with inorganic or organic acids or of its salts with optically active organic acids~~, characterized in that~~ wherein:

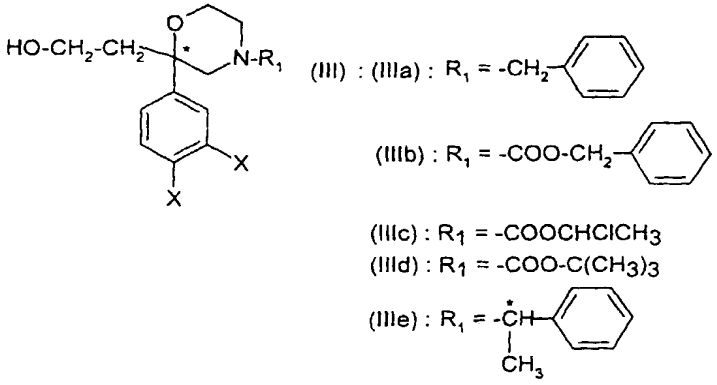
a) a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:





in which X is as defined for a compound of formula (I) and R_1 represents an N-protecting group chosen from a benzyl group, a benzyloxycarbonyl group, a 1-chloroethyloxycarbonyl

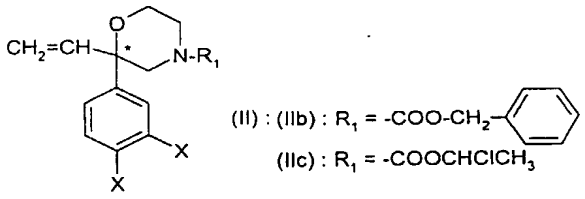
group, a *tert*-butyloxycarbonyl group or an α-methylbenzyl group, is converted to a compound, in the racemic form, in the form of a mixture of diastereoisomers or in the enantiomerically pure form, of formula:



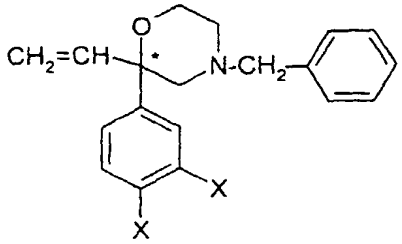
b) the compound of formula (III) thus obtained is deprotected;

c) if appropriate, when the compound of formula (I) thus obtained is in the racemic form, the enantiomers are separated, and, optionally, the enantiomerically pure compound of formula (I) is converted to one of its salts with inorganic or organic acids.

2. The process as claimed in claim 1 ~~, characterized in that~~ wherein a compound, in the enantiomerically pure form or in the racemic form, of formula:



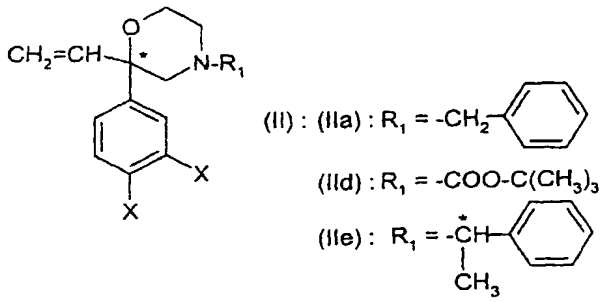
in which X represents a halogen atom and R_1 represents a benzyloxycarbonyl group or a 1-chloroethyloxycarbonyl group, is prepared by reaction of a compound, in the enantiomerically pure form or in the racemic form, of formula:



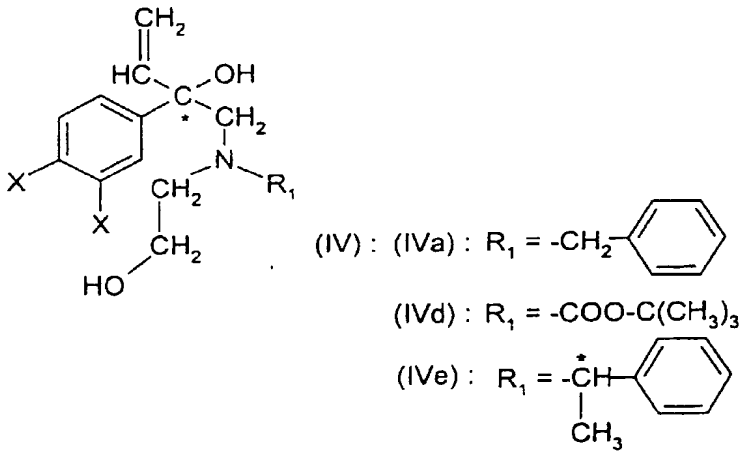
(IIa)

in which X is as defined for a compound of formula (II), with benzyl chloroformate or 1-chloroethyl chloroformate in the presence of a base, with or without solvent.

3. The process as claimed in ~~either of claims~~ claim 1 ~~and 2, characterized in that~~ wherein a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:

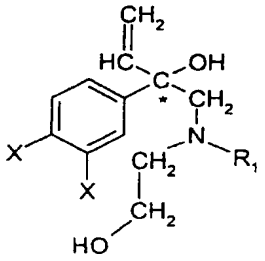


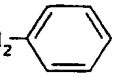
in which X represents a halogen atom and R_1 represents a benzyl group, a *tert*-butyloxycarbonyl group or an α-methylbenzyl group, of its optional salts with inorganic or organic acids, is prepared by cyclization of a compound, in the enantiomerically pure form, in the form of a mixture of diastereoisomers or in the racemic form, of formula:

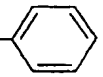


in which X and R_1 are as defined for a compound of formula (II), and, optionally, the compound of formula (II) thus obtained is converted to one of its salts.

4. The process as claimed in claim 3~~, characterized in that~~ wherein a compound, in the enantiomerically pure form, of formula:

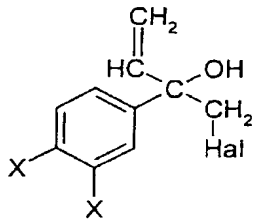


(IV) : (IVa) : $R_1 = -CH_2-$ 

(IVe) : $R_1 = -\overset{*}{C}H(CH_3)-$ 

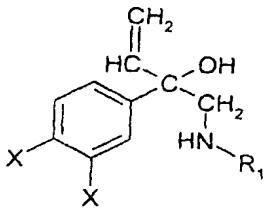
in which X represents a halogen atom and R_1 represents a benzyl group or an α-methylbenzyl group, of its salts with inorganic or organic acids, is prepared:

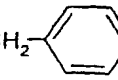
a) by reaction of a compound, in the racemic form, of formula:

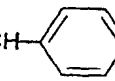


(V)

in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, with benzylamine or with R-(+)- or S-(-)-α-methylbenzylamine in the presence of a base in an inert solvent, to produce a compound, in the racemic form, of formula:



(VI) : (VIa) : $R_1 = -CH_2-$ 

(VIe) : $R_1 = -\overset{*}{C}H(CH_3)-$ 

b) by separation of the enantiomers or diastereoisomers of the compound of formula (VI) thus obtained;

c) by reaction of the enantiomerically pure compound of formula (VI) thus obtained:

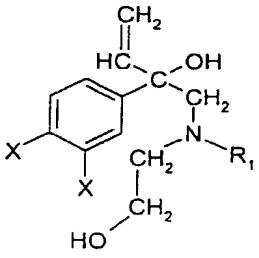
- either with ethylene oxide in the catalytic presence of an acid in an inert solvent;

- or with a compound of formula $Hal'CH_2-CH_2-O-R_2$ (XXI), in which R_2 represents an O-protecting group and Hal'represents a halogen atom, in the presence of a base in an inert solvent, followed by the deprotection of the O-protecting group;

and, optionally, by conversion of the enantiomerically pure compound of formula (IV) thus obtained to one of its salts with inorganic or organic acids.

5. The process as claimed in claim 4 ~~, characterized in that,~~ wherein in stage a), use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

6. The process as claimed in claim 3 ~~, characterized in that,~~ wherein a compound, in the racemic form or in the form of a mixture of diastereoisomers, of formula:



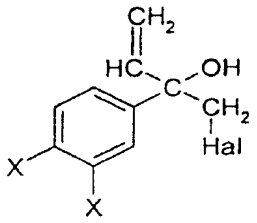
(IV) : (IVa) : R_1 = -CH_2- 

(IVd) : R_1 = -COO-$C(CH_3)_3$

(IVe) : R_1 = -$\overset{*}{C}H(CH_3)$- 

in which X represents a halogen atom and R_1 represents the benzyl group, the *tert*-butyloxycarbonyl group or the α-methylbenzyl group, or one of its optional salts with inorganic or organic acids, is prepared:

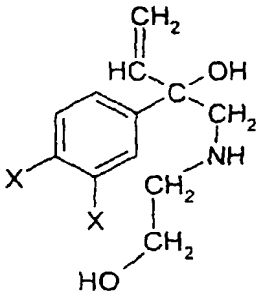
a) by reaction of a compound, in the racemic form, of formula:



(V)

in which X is as defined for a compound of formula (IV) and Hal represents a halogen atom, either with 2-(benzylamino)-1-ethanol or with 2-amino-1-ethanol or with (R)- or (S)-2-(α-methylbenzylamino)-1-ethanol, in the presence of a base and in an inert solvent, and, optionally, by conversion of the compound of formula (IVa) or (IVe) thus obtained to one of its salts with inorganic or organic acids;

b) if appropriate, when the compound of formula (V) is employed with 2-amino-1-ethanol in stage a), by reaction of the compound thus obtained, of formula:

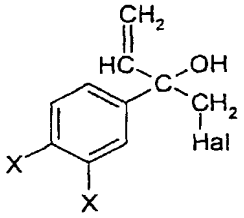


(IV'd)

with di-*tert*-butyl dicarbonate in the presence of a base and in an inert solvent, to produce the compound of formula (IVd).

7. The process as claimed in claim 6 ~~, characterized in that,~~ wherein use is made of a compound of formula (V) in which Hal represents a chlorine or bromine atom.

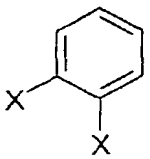
8. The process as claimed in ~~either of claims~~ claim 4 ~~and 6, characterized in that,~~ wherein a compound of formula:



(V)

in which X represents a halogen atom and Hal represents a halogen atom, is prepared:

a) by reaction of a compound of formula:

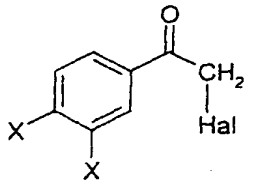


(VIII)

in which X is as defined for a compound of formula (V), with a compound of formula:

Hal'-CO-CH_2-Hal (IX)

in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:


(X)

b) by reaction of the compound of formula (X) thus obtained with a compound of formula:

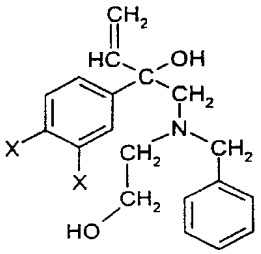
CH_2=CH-Mg-Hal" (XI)

in which Hal" represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce the compound of formula (V).

9. The process as claimed in claim 8 ~~, characterized in that,~~ wherein a compound of formula (V) in which Hal represents a chlorine or bromine atom is prepared.

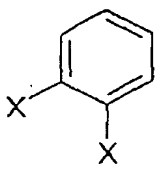
10. The process as claimed in claim 8 ~~, characterized in that,~~ wherein, in stage a), use is made of a compound of formula (IX) in which Hal' and Hal each independently represent a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal" represents a chlorine or bromine atom.

11. The process as claimed in claim 3 ~~, characterized in that,~~ wherein a compound, in the racemic form, of formula:


(IVa)

in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

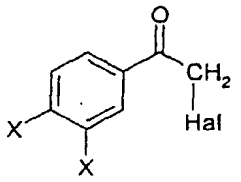
a) by reaction of a compound of formula:


(VIII)

in which X is as defined for a compound of formula (IVa), with a compound of formula:

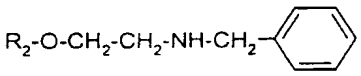
Hal'-CO-CH_2-Hal (IX)

in which Hal' and Hal represent a halogen atom, in the presence of a Lewis acid and in an inert solvent, to produce a compound of formula:



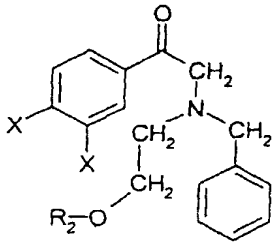
(X)

b) by reaction of the compound of formula (X) thus obtained with a compound of formula:



(XII)

in which R_2 represents an O-protecting group, in the presence of a base and in an inert solvent, to produce a compound of formula:

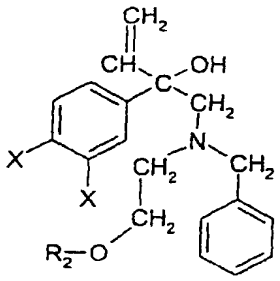


(XIII)

c) by reaction of the compound of formula (XIII) thus obtained with a compound of formula:

CH_2=CH-Mg-Hal" (XI)

in which Hal" represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound of formula:

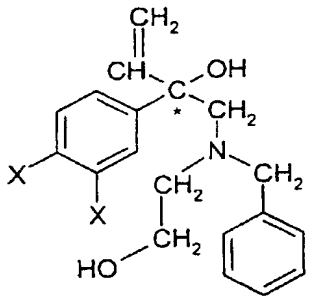


(XIV)

d) by deprotection of the compound of formula (XIV) and, optionally, by conversion of the compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

12. The process as claimed in claim 11 ~~, characterized in that,~~ wherein, in stage a), use is made of a compound of formula (IX) in which Hal and Hal' each independently represent a chlorine or bromine atom, in stage b), use is made of a compound of formula (XII) in which R_2 represents a tetrahydropyran-2-yl group, and, in stage c), use is made of a compound of formula (XI) in which Hal" represents a chlorine or bromine atom.

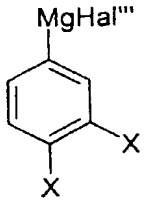
13. The process as claimed in claim 3 ~~, characterized in that,~~ wherein a compound, in the enantiomerically pure form, of formula:



(IVa)

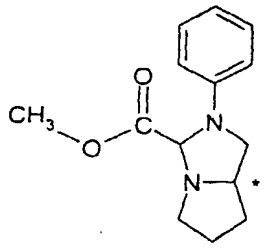
in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

b) by reaction of a compound of formula:



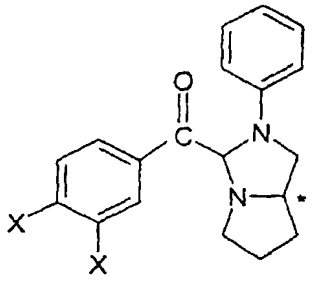
(XV)

in which X is as defined for a compound of formula (IVa) and Hal'represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



(XVI)

in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

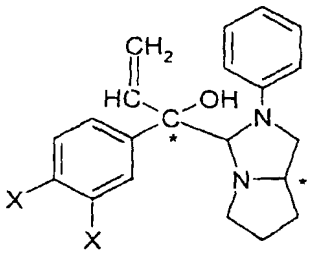


(XVII)

b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:

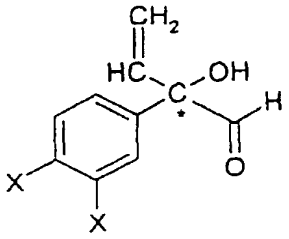
CH_2=CH-Mg-Hal" (XI)

in which Hal" represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



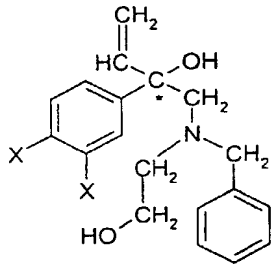
(XVIII)

c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:


(XIX)

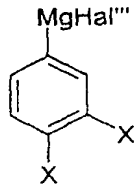
d) by reaction of the compound of formula (XIX) thus obtained with 2-(benzylamino)-1-ethanol in the presence of an acid in an inert solvent, then reduction of the iminium salt formed as an intermediate by means of a reducing agent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) to one of its salts with inorganic or organic acids.

14. The process as claimed in claim 3 ~~, characterized in that,~~ wherein a compound, in the enantiomerically pure form, of formula:

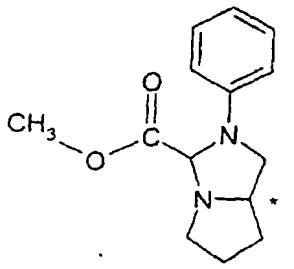

(IVa)

in which X represents a halogen atom, or one of its salts with inorganic or organic acids, is prepared:

a) by reaction of a compound of formula:

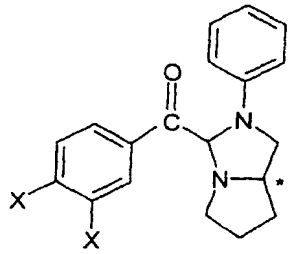

(XV)

in which X is as defined for a compound of formula (IVa) and Hal'represents a halogen atom, with methyl (R)- or (S)-2-phenylhexahydropyrrolo[1,2-c]imidazole-3-carboxylate, of formula:



(XVI)

in the presence of magnesium chloride in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:

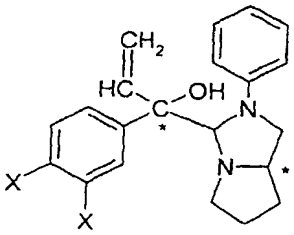


(XVII)

b) by reaction of the compound of formula (XVII) thus obtained with a compound of formula:

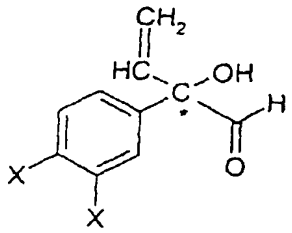
CH_2=CH-Mg-Hal" (XI)

in which Hal" represents a halogen atom, in an inert solvent, followed by hydrolysis, to produce a compound, in the enantiomerically pure form, of formula:



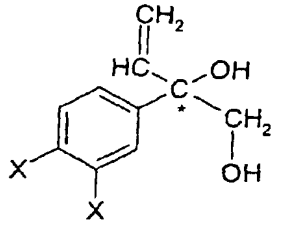
(XVIII)

c) by hydrolysis of the compound of formula (XVIII) thus obtained by the action of an acid in an inert solvent as a mixture with water, to produce a compound, in the enantiomerically pure form, of formula:



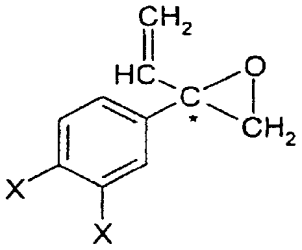
(XIX)

d) by reduction of the compound of formula (XIX) thus obtained by means of a reducing agent in an inert solvent, to produce a compound of formula:



(XX)

e) by cyclization of the compound of formula (XX) thus obtained, to produce a compound, in the enantiomerically pure form, of formula:



(VII)

f) by reaction of the compound of formula (VII) thus obtained with 2-(benzylamino)-1-ethanol in the presence of a base and in an inert solvent and, optionally, conversion of the enantiomerically pure compound of formula (IVa) thus obtained to one of its salts with inorganic or organic acids.

15. The process as claimed in ~~either of claims~~ claim 13 ~~and 14, characterized in that,~~ wherein, in stage a), use is made of a compound of formula (XV) in which Hal'represents a chlorine or bromine atom and, in stage b), use is made of a compound of formula (XI) in which Hal" represents a chlorine or bromine atom.

16. The process as claimed in one of claims 1, 2, 3, 4, 6, 8, 11, 13 and 14~~, characterized in that~~ wherein compounds of formula (I), (IIa), (IIb), (IIc), (IId), (IIe), (IVa), (IVd), (IVe) or (V) in which X represent a chlorine atom or a fluorine atom are prepared.

Claims 32-34 have been added.